Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of the Claims

1. (Original) A method for generating a collection of cells suitable as a recombinant polyclonal manufacturing cell line, said method comprising:

a) providing a library of vectors comprising a population of variant nucleic acid sequences, wherein each of said vectors comprises 1) one single copy of a distinct nucleic acid sequence encoding a distinct member of a polyclonal protein comprising distinct members that bind a particular antigen and 2) one or more recombinase recognition sequences;

b) introducing said library of vectors into a host cell line, wherein the genome of each individual cell of said host cell line comprises recombinase recognition sequences, matching those of the vector, at a single specific site in its genome;

c) ensuring the presence in said cells of one or more recombinases so that the variant nucleic acid sequences of step (a) are integrated site-specifically in the cells of the host cell line, where said one or more recombinases is/are either i) expressed by said cells into which said nucleic acid sequence is introduced; ii) operatively encoded by the vectors of step a; iii) provided through expression from a second vector; or iv) provided to the cell as a protein; and

d) selecting cells comprising an integrated copy from said library of variant nucleic acid sequences.

2. (Original) The method according to claim 1, wherein the polyclonal protein is not naturally associated with said collection of cells.

3. (Original) The method according to claim 1 or 2, wherein said polyclonal protein is a polyclonal antibody or antibody fragment.

4. (Original) The method according to claim 1 or 2, wherein said polyclonal protein is a polyclonal T cell receptor or T cell receptor fragment.

5. (Currently amended) The method according to ~~any one of the preceding claims~~ claim 1, wherein said library of vectors is introduced into said host cell line by bulk transfection of a collection of said host cells with said library of vectors.

6. (Currently amended) The method according to ~~any one of claims 1-4~~ claim 1, wherein said library of vectors is introduced into said host cell line by semi-bulk transfection of aliquots of said host cells with fractions comprising 5 to 50 individual vectors of said library of vectors, and said cells are pooled to form a collection of cells suitable as a recombinant polyclonal manufacturing cell line prior or subsequent to the selection of step (d).

7. (Currently amended) The method according to ~~any one of claims 1-4~~ claim 1, wherein said library of vectors for site-specific integration is introduced into said host cell line by transfecting said host cells separately with individual members of said library of vectors, and said cells are pooled to form a collection of cells suitable as a recombinant polyclonal manufacturing cell line prior or subsequent to the selection of step (d).

8. (Currently amended) The method according to ~~any one of the preceding claims~~ claim 1, wherein the population of variant nucleic acids in step (a) are isolated or identified by the aid of a screening procedure that enables identification and/or isolation of nucleic acids that encode protein which bind said particular antigen.

9. (Original) The method according to claim 8, wherein the screening procedure includes a biopanning step and/or an immunodetection assay.

10. (Original) The method according to claim 8 or 9, wherein said screening procedure is selected from the group consisting of phage display, ribosome display, DNA display, RNA-peptide display, covalent display, bacterial surface display, yeast surface display, eukaryotic virus display, ELISA and ELISPOT.

11. (Currently amended) The method according to ~~any one of the preceding claims~~ claim 1, wherein said library of variant nucleic acid sequences comprises at least 3 variant nucleic acid sequences.

12. (Currently amended) The method according to ~~any one of the preceding claims~~ claim 1, wherein individual members of said library of variant nucleic acid sequences are integrated in a single predefined genomic locus of individual cells in said collection of cells, said locus being capable of mediating high-level expression of each member of said recombinant polyclonal protein.

13. (Currently amended) The method according to ~~any one of the preceding claims~~ claim 1, wherein each distinct nucleic acid sequence comprises a pair of gene segments that encode a member of a polyclonal protein comprised of two different polypeptide chains.

14. (Original) The method according to claim 13, wherein said pair of gene segments comprise an anti-body heavy chain variable region encoding sequence and an antibody light chain variable region encoding sequence.

15. (Original) The method according to claim 13, wherein said pair of gene segments comprise a T cell receptor alpha chain variable region encoding sequence and a T cell receptor beta chain variable region encoding sequence.

16. (Original) The method according to claim 13, wherein said pair of gene segments comprise a T cell receptor gamma chain variable region encoding sequence and a T cell receptor delta chain variable region encoding sequence.

17. (Currently amended) The method according to ~~any one of the preceding claims~~ claim 1, wherein said library of variant nucleic acid sequences comprises a naturally occurring diversity located within the variant nucleic acid sequences.

18. (Original) The method according to claim 17, wherein the naturally occurring diversity is located in CDR regions, present in said variant nucleic acid sequences.

19. (Currently amended) The method according to ~~any one of the preceding claims~~ claim 1, wherein said collection of cells is derived from a mammalian cell fine or cell type.

20. (Original) The method according to claim 19, wherein said mammalian cell line is selected from the group consisting of Chinese hamster ovary (CHO) cells, COS cells, BHK cells, YB2/0, NIH 3T3, myeloma cells, fibroblasts, HeLa, HEK 293, PER.C6, and cell lines derived thereof.

21. (Original) A method for the manufacture of a polyclonal protein, wherein said polyclonal protein comprises distinct members that bind a particular antigen, said method comprising:

a) providing a collection of cells comprising a library of variant nucleic acid sequences, where each of said nucleic acid sequences encode a distinct member of said polyclonal protein and where each of said nucleic acid sequences are integrated at the same, single site of the genome of each individual cell in said collection of cells;

b) culturing said collection of cells under conditions facilitating expression of said polyclonal protein; and

c) recovering said expressed polyclonal protein from the cell culture cells or cell culture supernatant.

22. (Currently amended) The method according to ~~claims~~ claim 21, wherein the collection of cells in step (a) is generated according to ~~the method of any one of claims 1-20.~~ a method for generating a collection of cells suitable as a recombinant polyclonal manufacturing cell line, said method comprising:

a) providing a library of vectors comprising a population of variant nucleic acid sequences, wherein each of said vectors comprises 1) one single copy of a distinct nucleic acid sequence encoding a distinct member of a polyclonal protein comprising distinct members that bind a particular antigen and 2) one or more recombinase recognition sequences;

b) introducing said library of vectors into a host cell line, wherein the genome of each individual cell of said host cell line comprises recombinase recognition sequences, matching those of the vector, at a single specific site in its genome;

c) ensuring the presence in said cells of one or more recombinases so that the variant nucleic acid sequences of step (a) are integrated site-specifically in the cells of the host cell line, where said one or more recombinases is/are either i) expressed by said cells into which said nucleic acid sequence is introduced; ii) operatively encoded by the vectors of step a; iii) provided through expression from a second vector; or iv) provided to the cell as a protein; and

d) selecting cells comprising an integrated copy from said library of variant nucleic acid sequences.

23. (Original) The method according to claim 21 or 22, wherein the polyclonal protein is not naturally associated with said collection of cells.

24. (Currently amended) The method according to ~~any one of claims 21-23~~ claim 21, wherein the library of variant nucleic acids in step (a) are isolated or identified in an earlier step by the aid of a screening procedure that enables identification and/or isolation of nucleic acids that encode protein which bind said particular antigen.

25. (Original) The method according to claim 24, wherein the screening procedure includes a biopanning step and/or an immunodetection assay.

26. (Original) The method according to claim 24 or 25, wherein said screening procedure is selected from the group consisting of phage display, ribosome display, DNA display, RNA-peptide display, covalent display, bacterial surface display, yeast surface display, eukaryotic virus display, ELISA, and ELISPOT.

27. (Currently amended) The method according to ~~any one of claims 21-26~~ claim 21, wherein said polyclonal protein is a polyclonal antibody or antibody fragment.

28. (Currently amended) The method according to ~~any one of claims 21-26~~ claim 21, wherein said polyclonal protein is a polyclonal T cell receptor or T cell receptor fragment.

29. (Currently amended) The method according to ~~any one of claims 21-28~~ claim 21, wherein the relative expression levels of the variant nucleic acid sequences are monitored.

30. (Original) The method according to claim 29, wherein said expression levels are monitored at mRNA level and/or protein level.

31. (Original) The method according to claim 29 or 30, wherein the culturing in step (b) is terminated at the latest when the relative expression levels are outside a predetermined range.

32. (Original) A recombinant polyclonal manufacturing cell line comprising a collection of cells transfected with a library of variant nucleic acid sequences, wherein each cell in the collection is transfected with and capable of expressing one member of the library, which encodes a distinct member of a polyclonal protein that binds a particular antigen and which is located at the same single site in the genome of individual cells in said collection, wherein said nucleic acid sequence is not naturally associated with said cell in the collection.

33. (Original) The recombinant polyclonal manufacturing cell line according to claim 32, wherein said library of variant nucleic acid sequences encodes a polyclonal antibody or antibody fragment having a naturally occurring diversity among the individual members of said polyclonal anti-body or antibody fragments.

34. (Original) The recombinant polyclonal manufacturing cell line according to claim 32, wherein said library of variant nucleic acid sequences encodes a polyclonal T cell receptor or T cell receptor fragment having a naturally occurring diversity among the individual members of said polyclonal T cell receptor or T-cell receptor fragment.

35. (Currently amended) The recombinant polyclonal manufacturing cell line according to ~~any one of claims 32-34~~ claim 32, wherein said collection of cells is derived from a mammalian cell line or cell type.

36. (Original) The recombinant polyclonal manufacturing cell line according to claim 35, wherein said mammalian cell line is selected from the group consisting of Chinese hamster ovary (CHO) cells, COS cells, BHK cells, YB2/0, NIH 3T3, myeloma cells, fibroblasts, HeLa, HEK 293, PER.C6, and derivative cell lines thereof.

37. (Original) A library of vectors for site-specific integration comprising a population of naturally occurring variant nucleic acid sequences, wherein each of said vectors comprises 1) one copy of a distinct nucleic acid sequence encoding a distinct member of a polyclonal protein that binds a particular antigen and 2) one or more recombinase recognition sequences.

38. (Original) The library according claim 37, wherein said population of naturally occurring variant nucleic acid sequences encode a polyclonal antibody or antibody fragment.

39. (Original) The library according claim 37, wherein said population of naturally occurring variant nucleic acid sequences encode a polyclonal T cell receptor T cell receptor fragment.

40. (Currently amended) The library according to ~~any one of claims 37-39~~ claim 37, wherein each member of said library of vectors further comprises a recombinase encoding nucleic acid sequence.

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48. (New) A collection of cells comprising a library of variant nucleic acid sequences, where each of said nucleic acid sequences encodes a distinct member of a polyclonal protein comprising distinct members that bind a particular antigen and where each of said nucleic acid

sequences is integrated at the same single site of the genome of each individual cell in said collection of cells.

49. (New) The collection of cells according to claim 48, wherein the library of variant nucleic acid sequences is a library, wherein said library is a library of vectors for site-specific integration comprising a population of naturally occurring variant nucleic acid sequences, wherein each of said vectors comprises 1) one copy of a distinct nucleic acid sequence encoding a distinct member of a polyclonal protein that binds a particular antigen and 2) one or more recombinase recognition sequences.

50. (New) The collection of cells according to claim 48 or 49, wherein at least 50% of the encoding sequences originally present in the library can be identified as different individual members of the final polyclonal protein expressed from said collection of cells.

51. (New) A polyclonal antibody expressing cell line transfected with a library of pairs of V_H and V_L gene segments, wherein each cell in the cell line is transfected with and capable of expressing one V_H and V_L gene pair of the library, which encodes a distinct member of a polyclonal antibody that binds a particular antigen and which is located at the same single site in the genome of individual cells in said cell line, wherein said nucleic acid sequence is not naturally associated with said cell in the collection.

52. (New) The cell line according to claim 48, wherein the library of pairs of V_H and V_L gene segments is a library, wherein said library is a library of vectors for site-specific integration comprising a population of naturally occurring variant nucleic acid sequences, wherein each of said vectors comprises 1) one copy of a distinct nucleic acid sequence encoding a distinct member of a polyclonal protein that binds a particular antigen and 2) one or more recombinase recognition sequences and further wherein said population of naturally occurring variant nucleic acid sequences encode a polyclonal antibody or antibody fragment.